Elevated Homocysteine Levels and Disease Severity in Patients with Sickle Cell Anaemia: A Lagos cohort study (2014–2015)

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Abstract

Background: Hyperhomocysteinemia has been linked to the pathogenesis and severity of several conditions. Recent studies suggest its potential role in the clinical course and severity of sickle cell anaemia (SCA). This study examines the possible relationship between elevated homocysteine levels and disease severity in Nigerian patients with sickle cell anaemia.

Methods: This was a descriptive cross-sectional study conducted among adult patients with SCA attending Lagos University Teaching Hospital. A total of 84 patients were recruited and categorised into three clinical groups: steady-state, vaso-occlusive crises (VOC) and hyperhemolytic crises (HHC). Each participant's overall disease severity was assessed using a modified severity scoring system that incorporated both clinical and laboratory parameters. Data were collected using a structured study proforma. Serum homocysteine levels were measured using the enzyme-linked immunosorbent assay (ELISA) method. Statistical significance was set at $p < 0.05$.

Results: Participants' mean age was 24.9 (standard deviation 5.5) years. The mean serum homocysteine was higher among participants in HHC (13.1 ± 5.4 µmol/L) than those in VOC (11.9 ± 4.5 µmol/L) or steady-state (10.3 ± 2.3 µmol/L) (p = 0.073). About 20.0% of all participants had hyperhomocysteinemia. There was a statistically significant association between hyperhomocysteinemia prevalence and disease severity scores (p = 0.046). None of the participants with mild disease had hyperhomocysteinemia, while 25.9% and 17.6% of participants with moderate and severe disease had hyperhomocysteinemia.

Conclusion: The findings of this study suggest that elevated homocysteine levels may have an unmeasured effect on disease severity in patients with SCA.

Recommendation: This phenomenon is worth further exploration in prospective studies, so homocysteine levels can be monitored and managed to prevent morbidity among patients with SCA.

Keywords*: Anaemia; Sickle Cell Anaemia; Disease Severity; Homocysteine*
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Introduction

Sickle cell anaemia (SCA) is still a leading cause of morbidity and mortality worldwide [1,2]. Sub-Saharan Africa has the highest incidence of sickle cell anaemia, with Nigeria having the highest annual disease incidence [2]. About 2% of the entire population has sickle cell anaemia in Nigeria [2,3]. A population-level analysis estimates an average birth prevalence of 1.21% (95% CI 1.09–1.37) for haemoglobin SS (Hb SS) [3]. Sickle cell anaemia accounts for about 5% of deaths among children under five across Africa, increasing to over 9% in West Africa [2].

The clinical course and complications of SCA are often varied and multi-systemic [4]. The

disease severity is influenced by many factors, including foetal haemoglobin levels and genetic modifiers like BCL11A. The most frequent clinical manifestation of SCA is referred to as crises. This becomes evident at six to twelve months of age as presentation prior is modulated by elevated foetal haemoglobin, which serves as a protective factor [5,6]. Vaso-occlusive crisis (VOC) is a consequence of obstruction within the microcirculation by the sickle red blood cells, which leads to endothelial damage and end-organ ischaemic injury [7]. The effect of this condition negatively impacts patients, caregivers and families; frequent hospitalisation of patients may result in death [8].

Similar to the vascular damage seen in the pathogenesis of SCA, hyperhomocysteinemia, which is blood levels exceeding 15μmol/L, is believed to be injurious to the endothelium, causing endothelial cell dysfunction and thrombus formation [9]. This occurs either due to oxidative stress from free radicals seen during the oxidation of reduced homocysteine or due to prothrombotic effects of homocysteine [10]. As such, the unmeasured effect of hyperhomocysteinemia in the clinical course and severity of SCA has been proposed [10–12].

Hyperhomocysteinemia has been linked to genetic deficiencies of enzymes necessary in its metabolism and nutritional deficiencies such as folate, vitamin B6 and vitamin B12 [13]. Over the past few decades, homocysteine has been implicated in the pathogenesis of several diseases, including cardiovascular, neurologic and chronic kidney diseases [13–15]. For instance, an estimated 85% of patients with chronic kidney disease have hyperhomocysteinemia [15]. Additionally, different pathologic models have also highlighted the role of homocysteine dysfunction in the pathogenesis of stroke, Alzheimer's disease, Parkinson's disease and cognitive dysfunction [16,17]. Similarly, in recent studies, elevated homocysteine levels have also been mentioned in the pathogenesis of SCA [10].

The mechanism by which hyperhomocysteinemia occurs in SCA is explained by chronic hemolysis, which is a state of increased folate demand [18]. Insufficient folate intake, particularly when there is a hyperhemolytic crisis, results in a fall in plasma folate, red blood cell folate and erythroid blast folate levels [18]. Folate deficiency, in turn, results in the impairment of cells to convert homocysteine to methionine since the methyl group is the source of a unit of carbon atom required to convert homocysteine, which is usually generated from the trans-sulfuration pathway, back to methionine [9].

Elevated serum homocysteine is a known risk factor for vascular disease and may contribute to increased complications in patients with SCA. This study aimed to assess the prevalence of hyperhomocysteinemia among Nigerian SCA patients and to examine its potential association with disease severity. We hypothesised that higher homocysteine levels would correlate with greater disease severity in this population.

Methodology

Study design, setting and participants

This study used a descriptive cross-sectional design. Participants were recruited from the adult outpatient sickle cell clinic and the adult accident and emergency unit of the Lagos University Teaching Hospital (LUTH) between December 2014 and April 2015.

The study participants were patients diagnosed with SCA, and they were recruited using stratified random sampling into three arms. The first arm consisted of SCA patients who were in steady-state (Group A), the second arm consisted of SCA patients who were admitted on account of a painful vaso-occlusive crisis (Group B), and the third arm consisted of SCA patients who had a hyperhemolytic crisis (Group C). This stratification was to reduce selection bias and to

ensure that recruited participants were representative of the varying groups of SCA patients presenting at the centre.

Eligibility criteria

Patients aged ≥ 18 years who had a confirmed diagnosis of SCA (screened by sickling test and diagnosed by cellulose acetate electrophoresis at pH 8.4) and consented to participate in the study, were included. Patients with evidence of kidney disease, a history of thyroid dysfunction, or medications known to influence plasma homocysteine levels, such as phenytoin and methotrexate, were excluded.

Sample size

The sample size was calculated based on an effect size (mean plasma homocysteine 8.3 µmol/L ± 2.4 µmol/L) derived from a previous study [21], with 90% power and a 5% significance level. Based on this, the mean level in patients with sickle cell anemia was assumed as 10.7 µmol/L (8.3 + 1 × 2.4).

$$n = \frac{(u + v)^2 (\partial_1^2 + \partial_0)^2}{(\mu_1 - \mu_0)^2}$$

Substituting values ($u = 1.28$, $v = 1.96$, $\mu_1 = 10.7$, $\mu_0 = 8.3$, $\partial_1 = \partial_0 = 2.4$), this yielded a sample size of 21 for each arm: steady-state (Group A), vaso-occlusive crisis (Group B) and hyperhemolytic crisis (Group C). Additionally, a 10% attrition rate was calculated for the sample size.

The minimum sample size required for each arm of the study was 23. However, to maintain statistical power and allow for real world losses typical in acute clinical studies, we intentionally oversampled recruiting 27–30 participants per arm (providing an additional 10–20% buffer). The consecutive sampling method ensured proportional inclusion of patients across the disease states.

Data collection

The consecutive sampling method was utilised for patient recruitment. After consenting to participate in the study, data were collected using a pre-designed, pretested, interviewer-administered case report form. The case report form consisted of a biodata section and a medical history section. The case report form was pretested on 10 patients and minor adjustments were made to improve clarity and consistency, including clearer wording of medical history questions and the addition of standard international units. The overall Cronbach's alpha was 0.81, indicating good reliability. To enhance data validity and minimise recall bias, participant-reported histories were corroborated with case records.

Variables

For this study, steady-state was defined as a crisis-free period extending from at least three weeks since the last clinical event and three months or more since the last blood transfusion to at least one week before starting a new clinical event [19]. Vaso-occlusive crisis was defined as the onset of pain (bone, joint or multiple sites) that lasted for at least four hours, for which there was no other explanation other than vaso-occlusion and which required therapy with parenteral opioids in a medical setting [20]. Hyperhemolytic crisis was defined as a significant decrease in haemoglobin concentration from a steady-state value with evidence of increased red blood cell destruction (with or without reticulocytosis > 25% from baseline and/or presence of nucleated red blood cells in peripheral blood) in the absence of other identifiable causes of red cell destruction (splenic or hepatic sequestration) [20].

The primary outcome variable in this study was the disease severity indicators of study participants. The duration of reporting for disease severity indicators covered the 12 months preceding the study. Disease severity scoring of all participants was assessed by clinical history, physical examinations and laboratory investigation parameters and was based on a modified scoring system by Hedo [22]. The parameters included "number of crises in the past year" (0 – 1 crisis: score 0, 2 – 3 crises: score 1,

≥ 4: score 2), "number of transfusions in the past year" (1 – 2: score 1, ≥ 3: score 2], presence of "pneumonia" (score 1), "osteomyelitis" (score 1), "acute chest syndrome" (score 1), "dehydration" (score 1), "avascular necrosis of femur head" (score 1), "renal failure" (score 1), "pigment gallstone and jaundice" (score 1), "vaso-occlusive crises/pain" (no pain – score 0; localised pain – score 1; generalised pain – score 2) and "anaemia" (Hb ≥ 10g/dl – score 0; Hb ≥ 8 < 10 g/dl – score 1; Hb ≥ 6 < 8g/dl – score 2; Hb ≥ 4 < 6 g/dl – score 3; Hb < 4 g/dl – score 4). The total score was then classified into mild (≤ 3), moderate (4 – 7) and severe (> 7) scores.

Laboratory testing

Ten millilitres of venous blood were collected from each participant for laboratory analyses, which were conducted following standardised protocols to ensure reliability. For patients in crisis, samples were obtained within 24 hours of presentation at the facility. The analyses included haematological parameters [haemoglobin (Hb) level, packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width, white blood cell count, and platelet count], markers of haemolysis (reticulocyte production index, absolute reticulocyte count, lactate dehydrogenase, and indirect bilirubin), and serum homocysteine levels. Serum homocysteine was measured using an enzyme-linked immunosorbent assay (ELISA) with the Axis-Shield Diagnostics kit.

Homocysteine levels of study participants served as the predictor of the study outcome. The reference range for normal homocysteine was set at 5-15µmol/L [23]. Participants were also evaluated for the presence or absence of hyperhomocysteinemia and the relationship between laboratory factors and this outcome. Serum homocysteine level greater than 15µmol/L was defined as hyperhomocysteinemia [23].

Statistical methods

Data were entered and cleaned using the Microsoft Excel Sheet. Participants were followed up to ensure there was no missing data. Data were analysed using SPSS Version 28.0. Univariate analysis was presented using means and standard deviation (SD) as measures of centrality and dispersion. Categorical variables were presented as frequencies and percentages. Comparison of means was carried out using the Student's T-test, while the Chi-square test or Fisher's exact test (when expected cell values were less than five) was used to compare categorical variables. The level of statistical significance was defined as $p < 0.05$ in all cases.

Ethical approval

The Lagos University Teaching Hospital's Health Research and Ethics Committee approved the study protocol (ADM/DCST/HREC/APP/1740), and all participants gave written informed consent before being recruited into the study. The participants were assured of confidentiality of their data.

Results

Of the 104, patients approached for inclusion in the study, 95 met the inclusion criteria and were enrolled. Six patients withdrew consent and were excluded from the study, and five had incomplete or missing data. Eighty-four participants with sickle cell anaemia were, therefore, included in the final analysis. Table 1 presents the baseline demographic characteristics of the 84 participants with SCA enrolled in the study, stratified into three clinical groups: steady-state (n = 25), vaso-occlusive crisis (VOC; n = 30), and hyperhaemolytic crisis (HHC; n = 29). The mean age of participants was 24.9 ± 5.5 years, with ages ranging from 18 to 41 years. There was no significant age difference among the three groups: steady-state (24.9 ± 5.2 years), VOC (24.9 ± 6.0 years) and HHC (24.9 ± 5.3 years), p = 1.000.

Additionally, there were more male than female study participants (51.2% vs 48.8%), p = 0.407.

In the steady-state group, females were more represented (60.0%), while males predominated slightly in the VOC (56.7%) and HHC (55.2%) groups. Among all participants, 13 (15.5%), 54 (64.3%) and 17 (20.2%) had mild, moderate and severe disease severity scores, respectively.

The mean (± SD) homocysteine levels for all participants were 11.8 ± 4.5 µmol/L. The mean serum homocysteine was higher among participants in hyperhemolytic state (13.1 ± 5.4 µmol/L) compared to those in vaso-occlusive crises (11.9 ± 4.5 µmol/L) or in steady-state (10.3 ± 2.3 µmol/L). The mean serum homocysteine level in patients in all three groups did not significantly differ (p = 0.073).

Table 2 shows the distribution of hyperhomocysteinemia among patients with sickle cell anaemia based on their clinical state (steady-state, vaso-occlusive crises and hyperhemolytic crises) and disease severity (mild, moderate, and severe). About 20.0% of all participants had hyperhomocysteinemia. Among patients in steady-state, none had elevated homocysteine levels, whereas 26.7% of those in vaso-occlusive crises and 31.0% in hyperhemolytic crises had hyperhomocysteinemia. The difference in prevalence across clinical states was statistically significant (p = 0.004).

In terms of disease severity, none of the patients with mild disease had elevated homocysteine levels, while 25.9% of those with moderate disease and 17.6% with severe disease had hyperhomocysteinemia. However, the difference across severity categories was not statistically significant (p = 0.113).

Of all study participants, 13 (15.5%), 54 (64.3%) and 17 (20.2%) had mild, moderate and severe disease severity scores, respectively. Table 3 summarises the comparison of disease severity indicators between participants with elevated serum homocysteine levels (n = 17) and those with normal levels (n = 67).

Table 1:
Baseline Information of Study Participants

Variable	Category	Steady-State (n = 25)	Vaso-Occlusive Crisis (n = 30)	Hyperhaemolytic Crisis (n = 29)	Total (N = 84)
Age (years)	Mean ± SD	24.9 ± 5.2	24.9 ± 6.0	24.9 ± 5.3	24.9 ± 5.5
Sex	Female	15 (60.0%)	13 (43.3%)	13 (44.8%)	41 (48.8%)
	Male	10 (40.0%)	17 (56.7%)	16 (55.2%)	43 (51.2%)

SD: Standard deviation; %: Percentage

Table 2:
Prevalence of Hyperhomocysteinemia by Clinical State and Disease Severity

Variables		Hyperhomocysteinemia Present, n = 17 (20.0%)	Hyperhomocysteinemia Absent, n = 67 (80.0%)	Fisher's Exact Test	p-value
Clinical State	Steady-state	0 (0.0%)	25 (100.0%)	11.175	0.004[a]
	Vaso-occlusive crises	8 (26.7%)	22 (73.3%)		
	Hyperhemolytic crises	9 (31.0%)	20 (69.0%)		
Disease Severity	Mild	0 (0.0%)	13 (100.0%)		
	Moderate	14 (25.9%)	40 (74.1%)	4.519	0.113[b]
	Severe	3 (17.6%)	14 (82.4%)		

[a]*p-value for the difference in hyperhomocysteinemia across clinical states*
[b]*p-value for the difference in hyperhomocysteinemia across disease severity levels*
%: Percentage

Participants with elevated homocysteine had a higher average number of clinic visits per year (2.4 ± 1.4) compared to those with normal homocysteine (1.8 ± 1.7), although this difference was not statistically significant (p = 0.219). They also experienced more vaso-occlusive crises annually (3.2 ± 3.0 vs. 2.6 ± 2.3; p = 0.346) and more hyperhemolysis crises per year (1.2 ± 0.9 vs. 0.9 ± 0.9; p = 0.244), but these differences were also not statistically significant. Additionally, the elevated homocysteine group had more frequent hospitalisations per year (2.3 ± 1.9 vs. 1.7 ± 1.7; p = 0.156), though this was also not statistically significant.

However, a statistically significant difference was observed in the disease severity score, which was higher among those with elevated homocysteine levels (5.7 ± 1.1) compared to those with normal levels (4.6 ± 2.2), with a p-value of 0.046.

The mean haemoglobin, packed cell volume and platelet count in participants with hyperhomocysteinemia were lower than those with normal homocysteine levels, although this difference was not statistically significant (*Table 4*).

Table 3:
Association between Disease Severity Indicators and the prevalence of Hyperhomocysteinemia among Study Participants

Variable	Hyperhomocysteinemia Present, n = 17 Mean ± SD	Hyperhomocysteinemia Absent, n = 67 Mean ± SD	p-value
Clinic visits per year	2.4 ± 1.4	1.8 ± 1.7	0.219
Vaso-occlusive crises per year	3.2 ± 3.0	2.6 ± 2.3	0.346
Hyperhemolysis crises per year	1.2 ± 0.9	0.9 ± 0.9	0.244
Hospitalisations per year	2.3 ± 1.9	1.7 ± 1.7	0.156
Disease severity score	5.7 ± 1.1	4.6 ± 2.2	0.046

SD: Standard deviation
p-values computed using independent t-tests; significance threshold set at $p < 0.05$

Table 4:
Haematological and Biochemical Parameters Associated with Homocysteine Level among Participants

Variable	Hyperhomocysteinemia Present, n = 17 Mean ± SD	Hyperhomocysteinemia Absent , n = 67 Mean ± SD	p-value
Haemoglobin (g/dL)	7.0 ± 1.4	7.7 ± 1.7	0.141
Packed cell volume (%)	20.9 ± 4.2	22.6 ± 4.1	0.140
Mean corpuscular volume (fl)	90.4 ± 7.8	88.4 ± 8.9	0.390
Mean corpuscular haemoglobin (pg)	30.4 ± 3.8	30.1 ± 7.8	0.885
Mean corpuscular haemoglobin concentration (g/dl)	33.6 ± 2.1	33.1 ± 2.0	0.402
Red cell distribution width (%)	21.1 ± 2.9	21.1 ± 2.5	0.938
White blood cell count (x 10^9/L)	12.9 ± 5.7	12.1 ± 5.6	0.575
Platelet count (x 10^9/L)	264. 4 ± 116.3	303.1 ± 115.1	0.230
Markers of Haemolysis			
Reticulocyte production index	3.4 ± 1.8	2.9 ± 1.5	0.255
Absolute Reticulocyte count (x10^9/L)	328.9 ± 183.9	282.8 ± 153.8	0.292
Lactate dehydrogenase (U/L)	717.4 ± 322.0	703.7 ± 255.9	0.853
Indirect bilirubin (mg/dl)	26.2 ± 19.9	30.8 ± 20.5	0.413

SD: Standard deviation
p-values computed using independent t-tests; significance threshold set at $p < 0.05$

Conversely, the mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width and white blood cell count in participants with hyperhomocysteinemia were higher than those with normal homocysteine levels. This difference was not statistically significant. (*Table 4*).

Regarding the association between the markers of hemolysis and homocysteinemia participants with hyperhomocysteinemia had higher reticulocyte production index, absolute reticulocyte count and lactate dehydrogenase than those with normal homocysteine levels. A converse pattern was noted with indirect bilirubin levels in both groups, although these differences were not statistically significant. (*Table 4)*,

Discussion

Several studies have documented abnormal homocysteine levels among individuals with SCA [9,12,24,25]. In the present study, 20.0% of participants had elevated homocysteine levels, which is notably lower than the 40.6% reported by Uche in a Nigerian study [10]. Nevertheless, the mean homocysteine (11.8 ± 4.5 µmol/L) aligns with earlier research showing higher levels in SCA patients compared to healthy controls [9,12,25]. Lowenthal reported a comparable mean homocysteine of 12.6 µmol/L (range:7.2 – 34.8) with significantly elevated levels in SCA cases relative to controls [12]. In another comparative Indian study by Sati' Abbas, a higher mean homocysteine level was reported in patients with SCA and sickle-thalassaemia compared to HbAA controls [25]. However, this difference was not significant ($p > 0.05$). In contrast, Olaniyi reported significantly lower homocysteine in Nigerian SCA patients compared to controls ($p < 0.001$) [9]. The authors attributed the inverse relationship to regular folic acid supplementation in SCA patients, which is known to lower homocysteine levels even in the absence of folate deficiency [9,26].

In the current study, it was interesting to note the difference in homocysteine levels depending on the disease state, with the highest levels seen in hyperhemolytic and vaso-occlusive crises. This pattern could be indicative of a potential role of homocysteine in SCA crisis state and, as such, is worth exploring within a larger population. Furthermore, although the mean levels of haemolytic markers did not differ significantly by homocysteine status, they were higher in patients with hyperhomocysteinemia.

Participants in the current study showed a lack of significant association between homocysteine levels and the frequency of hospitalisations, VOC or hyperhemolytic crises. This differs from the findings of Sati' Abbas who reported moderately elevated homocysteine (mean:44.52 ± 23µmol/L) and identified a significant positive correlation between serum homocysteine and VOC frequency [25]. They inferred that hyperhomocysteinemia contributes to the initiation of vaso-occlusive crisis through the occlusion of small blood vessels. The absence of significant association between homocysteine levels and the rate of hospitalisations, VOC or hyperhemolytic crises in the current study unlike the findings by Sati' Abbas may be due to differences in geographical location and patient population [25]. Regardless, this finding underscores the need to explore the potential role of elevated homocysteine in the occurrence and frequency of crisis episodes in individuals with SCA.

In the present study, patients with hyperhomocysteinemia had significantly higher disease severity scores than those with normal homocysteine levels. Similarly, elevated plasma homocysteine levels have been associated with more severe disease in SCA patients [27]. The study by Uche supports this observation by demonstrating a statistically significant association between serum homocysteine levels and disease severity scores in individuals with SCA, reinforcing the potential role of elevated

homocysteine in worsening disease burden, possibly through exacerbation of endothelial dysfunction and vaso-oclusion [10].

It is clear from the significant associations reported by these studies that elevated homocysteine may have an unmeasured significant role in the disease severity of patients with SCA. As such, it is worth factoring into the clinical management of these patients. While routine homocysteine screening may not be feasible in the Nigerian settings due to cost and resource constraints, it can be adapted for high-risk patients and research programs. Closer monitoring of routine folic acid and vitamin B supplementation, as well as assessing the nutritional status of SCA patients regularly may help mitigate homocysteine-induced vascular complications.

Study Limitations

The study's findings establish a useful baseline in the association between disease severity and homocysteine level in patients with SCA. However, its cross-sectional design makes it difficult to establish causality; as such, even if a significant association was reported, there is still a need for prospective studies on the subject to establish temporality. Additionally, there is a limited generalizability of study's findings given the relatively small sample size. On the other hand, recall bias was minimized by verifying participants' clinical history with case records, while systematic recruitment across the three clinical categories helped reduce selection bias and ensured a balanced representation.

Conclusion

There was a statistically significant association between disease severity and elevated homocysteine levels in participants with SCA. This significant finding reveals that homocysteine levels may serve as a biomarker for disease severity, aiding in risk stratification.

Recommendation

The association from this study is, therefore worth further review in prospective studies to establish causality since homocysteine levels can be monitored and managed clinically to prevent morbidity among these patients.

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Authors' contributions

- Adebukola Orolu: conceptualisation, design, the definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, manuscript preparation, manuscript editing and manuscript review.
- Titilope Adeyemo: conceptualisation, design, the definition of intellectual content, manuscript editing and manuscript review.
- Alani Akanmu: conceptualisation, design, the definition of intellectual content, manuscript editing and manuscript review.

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